

Uncertainties in the Micro/nano-Particles Induced Hyperthermia Treatment on Tumor Subject to External EM Field

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Abstract—Advancement of the recent micro/nano technology has stimulated the renaissance of using magnetic micro/nano particles embedded in biological tissues for the target tumor hyperthermia. As is well known, mathematical solutions of bioheat transfer involved in hyperthermia treatment are indispensable for computerized optimization of hyperthermia parameters. However, estimating the level of uncertainties associated with tissue temperature and thermal ablation area remains a major challenge. In this article, the uncertainties for the predicted temperatures of tissues due to approximate parameters were studied, based on numerical simulation of three-dimensional (3-D) quasi-steady state electromagnetic (EM) field and transient temperature response in biological tissues induced by the external EM field. Contributions of uncertainty from the tissue area permeated with micro/nano particles, the concentration and size of micro/nano particles, and the frequency and strength of the external alternating EM field were analyzed, and the uncertainty limits for temperature distributions in these cases were also estimated. The uncertainty analysis presented in this article is expected to serve as a significant guide for performing a highly efficient and also completely safe tumor hyperthermia using magnetic micro/nano particles.

Keywords—tumor hyperthermia; magnetic micro/nano particle; uncertainty analysis; treatment planning

I. INTRODUCTION

The possibility of treating cancer by artificially induced hyperthermia has led to the development of many different devices designed to heat malignant cells while sparing surrounding healthy tissue from burn injury [1]. Up to now, a variety of methods have been developed to induce temperature rises either locally in target tissue region, or over the whole body. Among them, magnetic micro/nano particles offer some attractive possibilities in tumor hyperthermia, which have controllable sizes ranging from a few nanometres up to tens of nanometers [2-4]. The magnetic micro/nano particles can be made to resonantly respond to a time-varying EM field, with advantageous results related to the transfer of energy from the exciting field to the micro/nano particles. This heat then conducts into the surrounding diseased tissue. A major advantage of EM hyperthermia using micro/nano particles lies in its ability to selectively ablate the intended target tissue and flexibly control the destruction process [5, 6].

The first application of magnetic materials for localized hyperthermia dates back to 1957 when Gilchrist et al [7] heated various tissue samples with 20–100 nm size particles of γ - Fe_2O_3 exposed to a 1.2 MHz magnetic field. Their idea was to treat

lymphatic metastases of large bowel cancer with heat by inducing micro/nano ferromagnetic particles to embolize in lymph nodes draining the primary cancer site and then applying an external alternating magnetic field to cause hysteretic heating of the particles. Since then, there have been numerous publications describing a variety of modalities using different types of micro/nano magnetic particles [8-11].

Although the technique of EM hyperthermia using micro/nano particles has a sound theoretical basis, routine medical use of this hyperthermia modality are still not available. This is partly due to that there is still a lack of quantitative understanding of the temperature profiles induced by the external EM field, especially lack of full understanding the uncertainties associated with tissue temperature due to approximate parameters used, which may impede the successful operation of this therapy. In this study, uncertainties for the predicted temperatures of tissues due to approximate parameters will be studied based on the numerical solution of 3-D EM field and transient temperature field during EM hyperthermia using micro/nano magnetic particles. The effect of concentration and size of micro/nano particles, tissue area permeated with micro/nano particles, and frequency and strength of EM field will be respectively investigated.

II. MATHEMATICAL MODEL AND ALGORITHM

The computation domain was taken as a $0.08\text{m} \times 0.08\text{m} \times 0.08\text{m}$ cube and depicted in Fig. 1, in which x denotes the tissue depth from the skin surface while y and z are along the surface. During calculation, the EM field in the tissue was solved by Laplace equation firstly; then the heat generation due to the EM dissipated power in tissues embedded with magnetic micro/nano particles was determined; after the heat generation in tissues was determined, the Monte Carlo algorithm was implemented to solve the transient 3-D bioheat transfer equation with space dependent thermal physiological parameters; finally, uncertainty analysis of tissue temperature was given based on the numerical solution of 3-D transient temperature field during EM hyperthermia.

A. EM field Model

Under the EM field, the potential φ inside the tissue can be determined through solving the source free Laplace equation:

$$\nabla \cdot [\varepsilon(\mathbf{X}) \cdot \nabla \varphi(\mathbf{X})] = 0 \quad (1)$$

This project was funded by the National Natural Science Foundation of China (Grants: 50576104 & 50575219).

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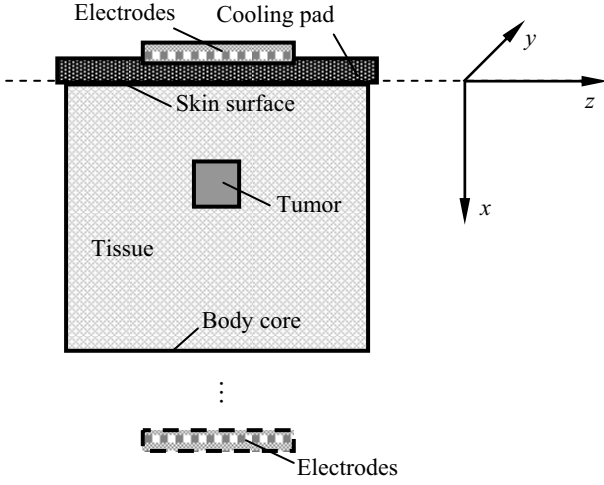


Figure 1. Schematic illustration of computation domain and EM induced hyperthermia configuration

where \mathbf{X} contains the Cartesian coordinates x, y and z ; and $\epsilon(\mathbf{X})$ is the dielectric constant permittivity of tissue.

The boundary conditions of EM field in tissue boundary can be written as [6]:

$$\phi = U, \mathbf{X} \in \Gamma, \quad \partial\phi/\partial n = 0, \mathbf{X} \notin \Gamma \quad (2)$$

where Γ denotes the surface area of electrodes.

After the potential ϕ is solved, then the electric field strength inside the tissue can be determined by:

$$\mathbf{E}(x, y, z) = -\nabla\phi(x, y, z) \quad (3)$$

Heat generation Q_{r1} due to the EM dissipated power in tissue without embedding magnetic micro/nano particles depends on the tissue conductivity σ and the electric field strength \mathbf{E} , and can be expressed as:

$$Q_{r1}(x, y, z) = \sigma |\mathbf{E}(x, y, z)|^2 / 2 \quad (4)$$

Heat generation Q_{r2} due to the EM dissipated power in tissue embedded with magnetic micro/nano particles can be approximately determined by [6]:

$$Q_{r2} = \frac{3nr^3\chi''}{4\mu_0 f R^2} |\mathbf{E}(x, y, z)|^2 + \left(1 - \frac{4}{3}n\pi r^3\right) \frac{\sigma}{2} |\mathbf{E}(x, y, z)|^2 \quad (5)$$

where n is the concentration of the micro/nano particles in tissue, r is the radius of the micro/nano particles, χ'' is the susceptibility of the magnetic nano-particles, μ_0 is the dielectric constant permeability of free space, f is the frequency of EM field, and R is the radius of the magnetic induction loop.

B. Thermal Model for Temperature Response in Tissue

The well-known Pennes equation [12] was used to model heat transfer in biological tissues:

$$\rho c \frac{\partial T(\mathbf{X}, t)}{\partial t} = \nabla \cdot k \nabla [T(\mathbf{X}, t)] - \omega_b(\mathbf{X}) \rho_b c_b T(\mathbf{X}, t) + \rho_b c_b \omega_b T_a + Q_m + Q_r \quad (6)$$

where ρ, c are the density and the specific heat of tissue, respectively; ρ_b, c_b denote density and specific heat of blood; k is the thermal conductivity, and $\omega_b(\mathbf{X})$ the space dependent blood perfusion; T_a the arterial temperature which is treated as a constant, and $T(\mathbf{X}, t)$ the tissue temperature; Q_m is the metabolic heat generation, and Q_r the spatial heat generation due to EM radiation.

To calculate the temperature field of tissues, the initial and boundary conditions can be prescribed as follows [13]:

$$\begin{cases} \nabla \cdot k \nabla [T_0(\mathbf{X})] - \omega_b(\mathbf{X}) c_b [T_a - T_0(\mathbf{X})] + Q_m(\mathbf{X}) = 0 \\ -k \frac{\partial T}{\partial y} = 0 & y = 0, L \\ -k \frac{\partial T}{\partial z} = 0 & z = 0, L \\ -k \frac{\partial T}{\partial x} = h_f (T - T_f) & x = 0 \\ T = T_c & x = L \end{cases} \quad (7)$$

where $L=0.08\text{m}$ is the width of the tissue domain in x, y , and z directions, h_f is the convection heat transfer coefficient, and T_f is the water temperature in cooling pad.

C. Numerical Algorithm

In this study, a newly developed Monte Carlo (MC) algorithm [13, 14] was applied to simulate the corresponding bioheat transfer problems. The particularly attractive feature of MC algorithm lies in that the solution at any desired point can be obtained independently from the solutions of the other points within the computation domain, which is an asset when temperature are needed at only some isolated sites.

A MC procedure begins by starting N random walks, referred to as the sample size. At the end of each random walk, the stochastic variable ξ is tallied. For the i th random walk, the stochastic variable is expressed as ξ_i , where $i=1, 2, \dots, N$. The description and derivation of stochastic variable were omitted here for brevity. Readers are referred to [13, 14] for more details. Following the completion of the N th random walk, the MC solution for $T(\mathbf{X}_0, t_0)$ can be written as

$$T(\mathbf{X}_0, t_0) = \frac{1}{N} \sum_{i=1}^N \xi_i \quad (8)$$

The above MC algorithm can then be used to solve the generalized bioheat transfer problems. The computer code

compiled in this article is revised from the code developed in our previous study [13], which had been validated through comparing the numerical results with the one-dimensional exact solution.

D. Uncertainty analysis

It is well accepted that both the analytical and numerical results cannot accord exactly with the experimentally measured results. Part of the reasons is due to the measurement error. More significant reason may come from the uncertainties implied in all sorts of parameters in heat transfer model used for predicting the tissue temperature [15]. In general, based on the heat transfer model, the tissue temperature during EM hyperthermia can be expressed by the following function:

$$T = f(w_1, w_2, \dots, w_M) \quad (9)$$

where w_1, w_2, \dots, w_M are M independent parameters such as blood perfusion rate, metabolic heat generation rate, heat capacity, and thermal conductivity of tissue, frequency and strength of EM field, concentration and size of micro/nano particles etc. Using the root sum-of-the-squares approach, the overall uncertainty of the tissue temperature can be given by

$$\Delta T = \sqrt{\left(\frac{\partial f}{\partial w_1} \Delta w_1\right)^2 + \left(\frac{\partial f}{\partial w_2} \Delta w_2\right)^2 + \dots + \left(\frac{\partial f}{\partial w_M} \Delta w_M\right)^2} \quad (10)$$

where $\partial f/\partial w$ and Δw are the sensitivity coefficient and uncertainty for parameter w . Equation (10) is a rigorous description of the uncertainty, which has been widely used for uncertainty analysis.

III. RESULTS AND DISCUSSION

In calculations, the typical thermal parameters of tissues were taken as: $\rho = \rho_b = 1000 \text{ kg/m}^3$, $c = c_b = 4200 \text{ J/kg}\cdot\text{°C}$, $k=0.5 \text{ W/m}\cdot\text{°C}$. The tumor domain was taken as $\Omega_t \subseteq [0.02\text{m} \leq x \leq 0.04\text{m}, 0.03\text{m} \leq y \leq 0.05\text{m}, 0.03\text{m} \leq z \leq 0.05\text{m}]$. The blood perfusion and metabolic rate in the tumor site often appear abnormally high, which were taken as [14]

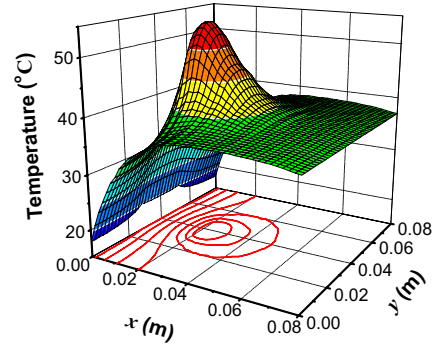
$$\begin{cases} \omega_b = 0.0005 \text{ ml/s/ml}, Q_m = 4200 \text{ W/m}^3 & x, y, z \notin \Omega_t \\ \omega_b = 0.002 \text{ ml/s/ml}, Q_m = 42000 \text{ W/m}^3 & x, y, z \in \Omega_t \end{cases} \quad (11)$$

For simplification, the magnetic micro/nano particles are assumed to be permeated uniformly into the tumor area. Fig. 2 shows the temperature distribution at $t=2000 \text{ s}$, $z=0.04 \text{ m}$ and transient temperature responses of tissues for a given case. It can be found from Fig. 2 that the peak temperature in the tumor region is about 53 °C while the temperature in the normal tissue is still below 42 °C . It indicates that most of the dissipated EM energy is absorbed by the tissue permeated with micro/nano particles during EM hyperthermia, and that this hyperthermia modality can be served as a good candidate for

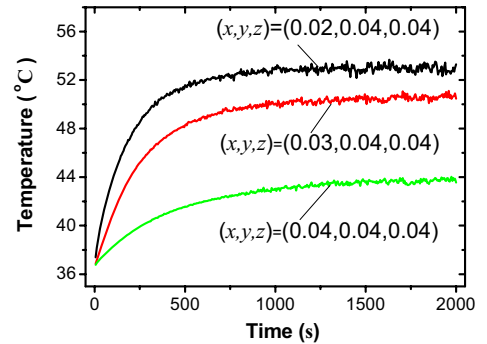
selective ablation of tumor. In fact, this feature is the major advantage of the current EM hyperthermia using magnetic micro/nano particles.

To maximize the killing effect to tumor while minimizing thermal injury on healthy tissues, optimal operation parameters should be determined before hyperthermia treatment. The process of optimizing the hyperthermia parameters is also termed as treatment planning, which is usually patient or tissue-specific. Currently, hyperthermia treatment planning is performed through numerical simulation of the heat transfer in biological tissues. As stated above, uncertainty of tissue temperature due to approximate parameters used cannot be avoided when performing numerical simulation. In order to achieve a favorable temperature distribution, uncertainty analysis on the tissue temperature is needed. In the present study, the uncertainty contributions from the tissue area permeated with magnetic micro/nano particles, the size and concentration of micro/nano particles, and the frequency and strength of EM field are particularly investigated, and the corresponding results are shown in Figs. 3-7 respectively. For illustration purpose, all the parameter uncertainties were defined at the same level for the following calculations

$$\Delta\Omega_p/\Omega_p = \Delta r/r = \Delta n/n = \Delta f/f = \Delta U/U = 20\% \quad (12)$$



(a) temperature distribution at $t=2000 \text{ s}$, $z=0.04 \text{ m}$



(b) Transient temperature responses at three specific positions

Figure 2. Results for the case with $U=10\text{V}$, $f=1.0\text{MHz}$, $n=1 \times 10^{21} \text{ m}^{-3}$, $r=10\text{nm}$

where Ω_p is the tissue domain permeated with magnetic micro/nano particles.

Fig. 3 shows the temperature uncertainty at $t=2000$ s, $z=0.04$ m contributed from the uncertainty of tissue area permeated with micro/nano particles. In calculation, the reference value of tissue domain permeated with micro/nano particles was the same as the tumor domain, and the reference value plus the uncertainty was taken as $\Omega_p + \Delta\Omega_p \subseteq [0.026\text{m} \leq x \leq 0.05\text{m}, 0.036\text{m} \leq y \leq 0.06\text{m}, 0.034\text{m} \leq z \leq 0.058\text{m}]$. From Fig. 3, it can be found that the largest temperature deviation due to the uncertainty of tissue domain permeated with micro/nano particles can be approximately to -12 °C. Figs. 4-7 depict the uncertainty contributions at $t=2000$ s, $z=0.04$ m resulted from the uncertainties in the size of micro/nano particles Δr , concentration of micro/nano particles Δn , the frequency of EM field Δf and strength of EM field ΔU respectively, in which the uncertainty values were taken as $\Delta r = 2$ nm, $\Delta n = 0.2 \times 10^{21} \text{ m}^{-3}$, $\Delta f = 0.2$ MHz, $\Delta U = 2$ V, and the reference values were taken as $r = 10$ nm, $n = 1 \times 10^{21} \text{ m}^{-3}$, $f = 1.0$ MHz, $U = 10$ V. It can be clearly seen from Figs. 4-7 that the corresponding largest temperature uncertainties resulted from the above given uncertainties of four parameters can be approximately to 12 °C, 3 °C, -3 °C, and 6 °C respectively.

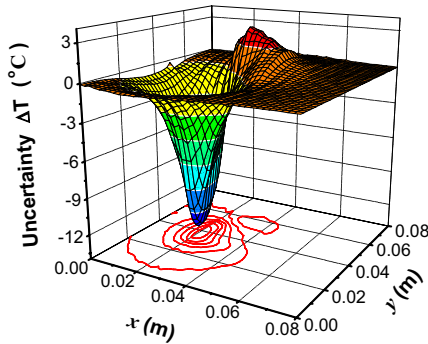


Figure 3. Temperature uncertainty from the tissue area permeated with micro/nano particles

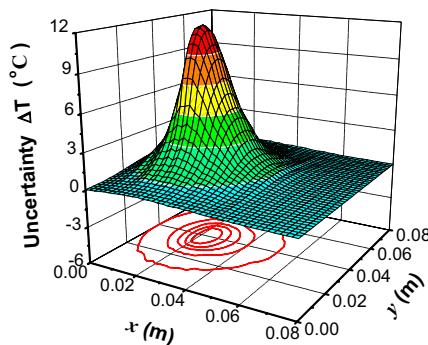


Figure 4. Temperature uncertainty from the size of micro/nano particles

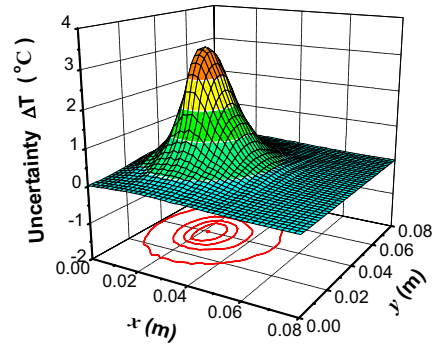


Figure 5. Temperature uncertainty from the concentration of micro/nano particles

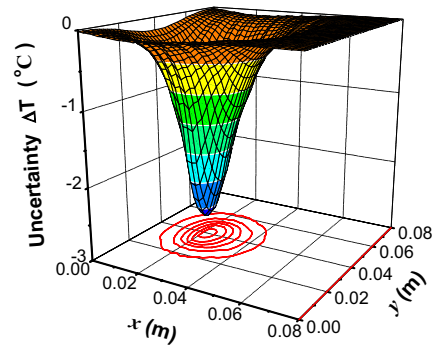


Figure 6. Temperature uncertainty from the frequency of EM field

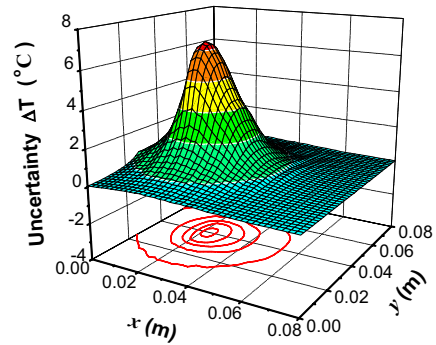


Figure 7. Temperature uncertainty from the strength of EM field

It is clearly indicated from the above figures that all of the largest temperature uncertainties occur at $(x, y) = (0.02 \text{ m}, 0.04 \text{ m})$. This may be caused by the largest temperature gradient near this area. In addition, it is also indicated that the heating effect of magnetic micro/nano particles induced hyperthermia depends heavily on the magnetic properties and concentration of the magnetic nano-particles, as well as the properties of the external alternating EM field because uncertainties (only 20%

of reference values) in such parameters can result in significant tissue temperature deviations.

As accepted by many researchers, regional hyperthermia is a rather promising modality of tumor treatment. The direct aim of regional hyperthermia is to achieve a favorable temperature distribution. Such a distribution can be characterized by the requirements that the tumor is locally heated to about or above 44 °C, but preferably not to any sane tissue. For this reason, treatment planning is necessary, which is patient or tissue-specific and usually performed through numerical simulation. It is well-known that, the real temperature responses of tissues subjected to heating cannot be exactly fitted by the theoretical modeling of bioheat transfer process. Part of the reasons is due to the measurement error of the apparatus. Uncertainties implied in the parameters of the bioheat model used for predicting the tissue temperature also do contribute significantly to the deviation between the theory and the experiments [15]. The concept of the uncertainty analysis is very useful in interpreting such practical applications in tissue temperature prediction in thermal medical engineering field. It is revealed in this study that the tissue temperature uncertainty due to the approximate parameters is large enough to cause invalid treatment and cannot be ignored. Therefore, it is important to consider the uncertainties when doing treatment planning for micro/nano-particles induced hyperthermia in which even a few degrees may cause serious problem. If without fully considering the tissue temperature uncertainty, the treatment plan thus designed may be not optimal.

IV. CONCLUSIONS

In this study, the temperature uncertainties in the micro/nano-particles induced hyperthermia treatment on tumor subject to external EM field due to approximate parameters were numerically investigated. The results indicate that the heating effect of magnetic micro/nano particles induced hyperthermia depends heavily on the parameters implied in bioheat transfer model, and that the tissue temperature uncertainty due to the approximate parameters cannot be ignored. It is thus concluded that it is necessary to perform uncertainty analysis when designing treatment plan for magnetic micro/nano particles induced hyperthermia. The uncertainty analysis presented in the present study is expected to be useful in treatment planning for regional hyperthermia to determine optimal operation parameters in such a way that a favorable tissue temperature distribution could be achieved.

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